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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,664	JENKINSON ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-78* is/are pending in the application.

4a) Of the above claim(s) *58,59 and 72-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-57,60-71,77 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 29, 2010 has been entered.

Status of Claims

Claims 48-78 are pending in the instant application. Claims 58-59 and 72-76 have been withdrawn as being drawn to inventions nonelected within traverse. See the reply filed on June 27, 2008. Accordingly, claims 48-57, 60-71, and 77-78 are currently under examination on the merits in the instant case.

Response to Arguments

Applicant's arguments with respect to claims 48-57, 60-71, and 77-78 filed with the RCE have been fully considered but are moot in view of the new ground(s) of rejection.

Claim Objections

Claim 49 is objected to because of the following informalities: It appears that the word "is" is necessary between the words "portion" and "selected" in line 2 for grammatical correction. Appropriate correction is required.

Claim 51 is objected to because of the following informalities: It appears that the word "part" in line 2 is unnecessary. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53 and 55-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "nascent" in claim 53 is a relative term which renders the claim indefinite. The term "nascent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "nascent" is normally understood to mean "novel" or "new". As such, some RNAs may be viewed as "nascent" by a person in 1996 but are in fact no longer "nascent" when viewed by a person in 2002. That is, the meaning of the term "nascent" in the context of "RNA" changes in relation to time, thus being a time-dependent, relative term. Hence, the term "nascent RNA" is not a constant, definite term but constantly changing term in the art as new RNAs are constantly being discovered. Hence, one of ordinary skill in the art cannot determine the metes and bounds pertaining to the claimed subject matter of claim 53.

Claims 55-56 recite the limitation "wherein the chromatin inactivation portion" in line 2. There is insufficient antecedent basis for this limitation in the claim because claim 50 recites "chromatin inactivation portions", not "chromatin inactivation portion".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 48-55, 61-71, and 77-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomescu et al. (*TRENDS in Molecular Medicine,* 2001, 17:554-559) in view of Opalinska et al. (*Nature Reviews,* 2002, 1:503-514, citation of record), Hoetelmans et al. (*Cell Death and Differentiation,* 2000, 7:384-392), and Kalderon et al. (*Cell,* 1984, 39:499-509).

The instant specification teaches that the modifying portion may be KRAB and that when a KRAB polypeptide is part of the molecule that is targeted to a selected gene by the nucleic acid

portion, the KRAB polypeptide is included within the term "chromatin inactivation portion.". See page 11.

Tomescu et al. teach that one can promote apoptosis of cancer/tumor cells with an antisense oligonucleotide targeted to an anti-apoptotic gene or a transcriptional repressor construct encoding the repressor peptide (e.g., PAX3-KRAB fusion peptide) that reduces anti-apoptotic gene expression (e.g., BCL2L1, also known as BCL-XI) when introduced into tumor cells. See the entire reference. Tomescu et al. do not teach using a combination product comprising the KRAB peptide fused with a TFO targeted to and inhibits an anti-apoptotic gene.

Opalinska et al. teach that an anti-bcl-2 antisense oligonucleotide promote apoptosis of cancer cells and that it can be combined with another pro-apoptotic agent such as a chemotherapeutic agent (e.g., decarbazine, mitoxantrone) for promoting apoptosis of cancer cells and for cancer treatment. They teach that triple-helix forming oligodeoxynucleotides (TFOs) also inhibit target expression by binding target DNA in a sequence-specific manner. See page 504; Tables 1 and 2.

Hoetelmans et al. teach that bcl-2 is expressed in the nuclei of breast cancer cells and that bcl-2 antisense oligonucleotide results in a reduction in the nuclear bcl-2 as well as cytoplasmic bcl-2. They teach that bcl-2 is associated with mitotic chromatin. They thus teach that the anti-apoptotic activity of bcl-2 occurs in the nuclear compartment as well as in the cytoplasmic compartment. See the entire reference.

Kalderon et al. teach that a nuclear localization signal sequence Pro-Lys-Lys-Lys-Arg-Lys-Val ("PKKKRKV") derived from SV40 promotes transportation of a molecule from the cytoplasm into the nucleus. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to promote apoptosis of cancer cells with a combination product comprising the PAX3-KRAB peptide fused with a TFO targeted to bcl-2.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success so as to further enhance the rate of cancer cell apoptosis, thereby improving the cancer treatment effects in a subject because both PAX3-KRAB peptide and bcl-2-targeting nucleic acid molecule were known to promote cancer (or tumor) cell apoptosis and because TFO was one of the target sequence-specific nucleic acid-based inhibitors known in the art. See *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980), wherein the court expressed the following: "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…[T]he idea of combining them flows logically from their having been individually taught in the prior art." Further, one of ordinary skill in the art would have been motivated to conjugate the "PKKKRKV" nuclear localization signal of Kalderon et al. to the fused, combination product in order to directly influence the cellular activities of PAX3-KRAB peptide and TFO targeted to bcl-2 in the cellular compartments wherein PAX3-KRAB and bcl-2 are expressed by delivering the product into the cellular compartment (nucleus) wherein the two elements function to promote apoptosis. In addition, since combination cancer therapeutic methods comprising administering different classes of anti-cancer agents (e.g., administering an anti-bcl-2 antisense oligonucleotide and decarbazine) were already art-recognized cancer treatment methods as taught by Opalinska et al., it would have been obvious to further administer a chemotherapeutic agent to a subject in addition to the combination product comprising the PAX3-KRAB peptide and the TFO targeting

bcl-2. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 48-57, 60-71, and 77-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buluwela et al. (WO 01/02019 A2, applicant's citation) in view of Wolffe et al. (WO 02/26960 A2, citation of record), Opalinska et al. (*Nature Reviews,* 2002, 1:503-514, citation of record), Hoetelmans et al. (*Cell Death and Differentiation,* 2000, 7:384-392), and Kalderon et al. (*Cell,* 1984, 39:499-509).

Buluwela et al. teach that one can suppress or inactivate target expression with an antisense oligonucleotide that binds to a target mRNA molecule, however, target gene suppression or inactivation by antisense technique requires "persistent expression of administration of the gene-inactivating agent." and therefore an alternate strategy to effectively inactivate target expression is in need. See page 2. They teach that one can inactivate target expression with "a polypeptide comprising a nucleic acid binding portion which binds to a site present in a eukaryotic genome and a chromatin inactivation portion" (see page 5), wherein chromatin inactivation portion preferably "facilitates histone deacetylation." (see page 8) or "facilitates recruitment of a HDAC complex" (see page 10), wherein the chromatin inactivation portion comprises binding motifs that are "sufficient to act as chromatin inactivation portions in the polypeptide of the invention" (see page 11) or the chromatin inactivation portion preferably is "PLZF or a portion thereof" (see page 31), wherein the nucleic acid portion and the chromatin inactivation portion are "fused" or "joined so that both portions retain their respective activities", wherein the two portions are can joined directly or indirectly via a linker (see page 17). They teach that HDAC (including HDAC1, HDAC2, HDAC3) can direct gene inactivation, wherein

HDAC recruits the assembly of PLZF, N-CoR, SMRT, MAD, SAP18, Rb, MeCpG2, and Sin3, wherein the gene inactivating complex mediates its gene inactivation through histone deacetylation. See pages 9-13.They teach that inactivation of oncogenes (e.g., mutant Ras, mutant Bcl-10) or genes involved in cancer is useful for medical treatment. See pages 31-32. They teach that one can formulate the fused construct as a pharmaceutical composition. See page 40. See also claims 1-11. Buluwela et al. do not teach promoting apoptosis in a cell with a fused construct comprising a polypeptide comprising a chromatin inactivation portion and a TFO targeted to an apoptosis-related gene.

Wolffe et al. teach, similar to Buluwela et al., that one can make a "fusion molecule" comprising at least two different subunit molecules operably or covalently linked in order to inhibit target expression/activity. They teach that the at least two different subunit molecules within the fusion molecule can be of the same kind or different types of molecules. For example, they teach that the fusion molecule is "a fusion between a triplex-forming nucleic acid and a polypeptide". See page 13. They teach that the fusion molecule can be used to target bcl-2. See pages 58-59.

Opalinska et al. teach that an anti-bcl-2 antisense oligonucleotide promote apoptosis of cancer cells and that it can be combined with another pro-apoptotic agent such as a chemotherapeutic agent (e.g., decarbazine, mitoxantrone) for promoting apoptosis of cancer cells and for cancer treatment. They teach that triple-helix forming oligodeoxynucleotides (TFOs) also inhibit target expression by binding target DNA in a sequence-specific manner. See page 504; Tables 1 and 2.

Hoetelmans et al. teach that bcl-2 is expressed in the nuclei of breast cancer cells and that bcl-2 antisense oligonucleotide results in a reduction in the nuclear bcl-2 as well as cytoplasmic

bcl-2. They teach that bcl-2 is associated with mitotic chromatin. They thus teach that the anti-apoptotic activity of bcl-2 occurs in the nuclear compartment as well as in the cytoplasmic compartment. See the entire reference.

Kalderon et al. teach that a nuclear localization signal sequence Pro-Lys-Lys-Lys-Arg-Lys-Val ("PKKKRKV") derived from SV40 promotes transportation of a molecule from the cytoplasm into the nucleus. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a fusion molecule comprising a TFO targeted to bcl-2, which is fused to a polypeptide comprising a chromatin inactivation portion of a HDAC complex component and deliver it to the nucleus of a cancer cell.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success so as to more effectively suppress the anti-apoptotic activity of bcl-2 in a cancer cell, thereby promoting the apoptosis of the cancer cell for cancer treatment in a subject, because the fusion molecule comprising a nucleic acid-based inhibitor (e.g., antisense oligonucleotide) fused to a polypeptide comprising a chromatin inactivation portion of a HDAC complex component was suggested to more effectively inactivate target expression compared to the nucleic acid-based inhibitor treatment alone as suggested by Buluwela et al., and because making "a fusion between a triplex-forming nucleic acid and a polypeptide" (see page 13) targeted to bcl-2 was suggested to be useful for inhibiting bcl-2 activity as taught by Wolffe et al., and because bcl-2 is an art-recognized anti-apoptotic gene, which is expressed in the nuclear compartment of a cancer cell, wherein the nuclear expression of bcl-2 was known to be inhibited with a nucleic acid targeted to bcl-2. Hence, one of ordinary skill in the art would have been motivated to conjugate the "PKKKRKV" nuclear localization signal of Kalderon et al. to the

fusion molecule in order to directly influence the cellular activities of the chromatin inactivation portion of a HDAC complex and the triplex-forming nucleic acid (TFO) targeted to bcl-2 in the cellular compartments wherein the HDAC complex and bcl-2 are expressed by delivering the product into the cellular compartment (nucleus) wherein the two portions (the chromatin inactivation portion and the TFO portion) function to promote apoptosis. In addition, since combination cancer therapeutic methods comprising administering different classes of anti-cancer agents (e.g., administering an anti-bcl-2 antisense oligonucleotide and decarbazine) were already art-recognized cancer treatment methods as taught by Opalinska et al., it would have been obvious to further administer a chemotherapeutic agent to a subject in addition to the fusion molecule. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 48-57, 60-63, 65-71, and 77-78 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 44-85 of copending Application No. 12/152,175. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the reference claims are drawn to a method of suppressing the expression of a gene comprising introducing a molecule having a nucleic acid binding portion and an expression repressor/modifying portion. Although the reference claims do not explicitly recite promoting apoptosis in a cell, the specification of 12/152,175 teaches that the methods of claims 44-85 read on cancer treatment methods by suppressing oncogene expression. See page 52. Hence, the reference claims inherently encompass the apoptosis promoting methods claimed in the instant case. Therefore, the scope of the instant claims and that of the reference claims overlap with each other and thus they are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 48-57, 60-71, and 77-78 are is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 44-85 of copending Application No. 12/152,175 in view of Opalinska et al. (*Nature Reviews,* 2002, 1:503-514, citation of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the reference claims are drawn to a method of suppressing the expression of a gene comprising introducing a molecule having a nucleic acid binding portion and an expression repressor/modifying portion. The primary difference between the two sets of claims is that the instant claims specifically recite suppressing bcl-2, thereby promoting apoptosis in a cell. As taught by Opalinska et al., it was known in the art that inhibiting bcl-2 promotes apoptosis in a cell and thus useful for cancer treatment. Given the broad interpretation of the reference claims, it is found that the reference claims in 12/152,175 encompass cancer treatment methods. As such, it would have been obvious to target bcl-2 with the nucleic acid binding portion when practicing the methods of the reference claims, and therefore, the instant claims and the reference claims are obvious variants of each other, hence are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi (Acting SPE) can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/Dana Shin/
Examiner, Art Unit 1635